REMARKS

Claims 50, 52, 55-63, 65-68, 70, 72-78, and 84 are pending in the application. Claims 1-49, 51, 53, 54, 64, 69, 71, and 79-83 have been cancelled without prejudice or disclaimer. Claims 52, 68, and 84 are amended. Following entry of the amendment, claims 50, 52, 55-63, 65-68, 70, 72-78, and 84 are pending in the application.

Support for the amendment of claims 52 and 84, is found in the claims and specification, as originally filed. Support for the amendment of claim 68 is found, for example, in the originally filed specification at page 14, lines 24-27.

Amendment of any claim herein is not to be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action, and was done to expedite prosecution of the application. Applicants make these amendments without prejudice to pursuing the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject mattered. Support for these amendments appears throughout the specification and claims as filed. No new matter is introduced by these amendments.

Drawings

Replacement drawings are being filed herewith. Applicants submit no new matter is added.

Objections to the Specification

Applicants have amended the paragraphs containing the typographical errors stated on page 3 of the Office Action to correct the typographical errors. No new matter is added.

Objection is made to the title of the invention as originally filed. In particular, the Office Action at page 3 indicates that "The title of the invention is not descriptive." Applicants respectfully disagree.

Applicants submit that the title fully complies with the requirements of 37 C.F.R. §1.72(a), which states:

> The title of the invention may not exceed 500 characters in length and must be as short and specific as possible. Characters that cannot be captured and recorded in the Office's automated information systems may not be reflected in the Office's records in such systems or in documents created by the Office. Unless the title is supplied in an application data sheet (§ 1.76), the title of the invention should appear as a heading on the first page of the specification.

From a plain reading of 37 C.F.R. §1.72(a), the rule nowhere requires that the title be "clearly indicative of the invention to which the claims are directed," as stated on page 3 of the Office Action. Instead, 37 C.F.R. §1.72(a) requires that a title be "as short and specific as possible." Although the claims are directed to GM-CSF and VEGF in inducing formation of new blood vessels, the invention is not so limited. The specification describes various embodiments of an invention that all relate to "Compositions and Methods for Modulating Vascularization," as indicated by the present title. Moreover, the present application is a divisional application and shares the same specification as the parent application, which discusses an embodiment of the invention. Thus, the title is concise and specific to the disclosure of the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection to the title.

Rejection under 35 U.S.C. §112, second paragraph

Claims 52, 68, and 84, and claims depending therefrom, are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Applicants respectfully disagree and traverse the rejection.

Claims 52 and 84 are allegedly indefinite for respectively reciting "to increase frequency" of endothelial progenitor cells (EPC) or "increasing [endothelial progenitor cell (EPC)] frequency." Specifically, the Office has alleged that it is unclear whether "frequency" refers to an increase in the frequency of circulating EPCs or an enhancement of mobilization.

Applicants submit that the specification clearly describes the terms "frequency of EPCs" and "mobilization of EPCs", and the relationship between them. As stated on page 6 of the Office Action, the specification describes an increase in the frequency of EPCs (page 34, line 29). For example, an increase in the frequency of EPCs by administration of GM-CSF is shown

by the experiments described in Example 3. Thus, the specification states that the increase in frequency is at least 20% as measured by a standard EPC isolation assay:

> In a particular embodiment of the method, the enhancement in EPC mobilization and particularly the increase in frequency of the EPCs is at least about 20% and preferably from between 50% to 500% as determined by a standard EPC isolation assay. That assay generally detects and quantifies EPC enrichment... [page 6, lines 11-15]

At the sentence spanning page 5, line 34 – page 6, line 1, the originally filed specification plainly states: "EPC mobilization is understood to mean a significant increase in the frequency and differentiation of EPCs as determined by assays disclosed herein." That is, an increase in the frequency of EPCs is indicative of EPC mobilization. In addition to an increase frequency of circulating EPCs, EPC mobilization is also demonstrated by other changes in EPCs, including an increase in their differentiation. Thus, the specification is clear regarding the meanings of the terms "frequency of EPCs" and "mobilization of EPCs", and how the two terms relate to one another. Thus, this basis for the indefiniteness rejection should be withdrawn.

The Office has also rejected claims 52 and 84 under 35 U.S.C. §112, second paragraph, as allegedly "being incomplete for omitting essential steps, such omission amounting to a gap between the steps." Applicants submit that it is clear that claims 52 and 84, directed to methods for inducing formation of new blood vessels in a mammal, at least include a step of administering as respectively recited in claims 52 and 84. Nevertheless, without acquiescing to the rejection and in order to expedite prosecution, Applicants have amended claims 52 and 84 to recite "thereby inducing the formation of new blood vessels in a mammal having chronic or acute ischemia." Therefore, Applicants respectfully request reconsideration of the rejection of claims 52 and 84 under 35 U.S.C. §112, second paragraph.

The Office has rejected claim 68 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for reciting "VEGF or GM-CSF is coadministered with at least one angiogenic protein." Applicants submit that it is clear that claim 68 requires an angiogenic protein be coadministered when either VEGF or GM-CSF are administered. That is, according to claim 68, any angiogenic protein, including VEGF or GM-CSF may be coadministered with either VEGF or GM-CSF. However, without in any way acquiescing to the reasoning underlying the rejection, and to expedite prosecution, Applicants have amended claim 68 to recite "at least one

additional angiogenic protein." Therefore Applicants respectfully request reconsideration of the rejection of claim 68 under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §112, first paragraph

Claims 50, 53, 55-63, 65-68, 70, 72-78 and 84 are rejected for allegedly failing to comply with the written description requirement. Applicants disagree with the rejection and request that it be withdrawn.

Applicants teach that the term "GM-CSF" as used in the specification is a protein having substantial identity to an amino acid sequence of human GM-CSF as disclosed, for example, in published international application WO 86/00639, [previously submitted in an Information Disclosure Statement mailed October 30, 2001; hereinafter "the '639 publication] (page 17, lines 1-6). The '639 publication, which is incorporated in its entirety by reference, describes the full length amino acid sequences of human GM-CSF polypeptides having biological activity at Figure 1. At page 17, lines 14-24, the specification also cites the disclosures of U.S. Patent Application No. 5,229,496 [previously submitted in an Information Disclosure Statement mailed October 30, 2001; hereinafter "the '496 publication], which are also incorporated by reference in their entirety. Thus, Applicants disclose GM-CSF and GM-CSF analogs as described in the '639 publication and the '496 publication.

Moreover, the '639 publication and the '496 publication teach a variety of assays for evaluating the functionality of any GM-CSF analog. In as much as the enablement and written description requirement are related under 35 U.S.C. §112, these disclosures, as well as that of the present specification, teach how to make GM-CSF analogs that are substantially identical and how to identify those that are functional. It is expected that any GM-CSF having substantial identity would be expected to work in the methods of the invention. As shown by Exhibit A and B, altering amino acid sequences of GM-CSF and identifying functional GM-CSF-analogs were well known in the art at the time of filing. "A patent specification need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

Moreover, because such experimentation to alter amino acid sequences of GM-CSF and identify functional GM-CSF analogs was common, this experimentation would be considered routine and not undue. In *In re Wands* 858 F.2d at 740, 8 USPQ2d at 1406, the Court held that

the specification was enabling with respect to the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known." MPEP §2164.01. Thus, Applicants' references to a protein having a sequence with substantial identity to a GM-CSF sequence would be within the grasp of one of skill in the art.

Again, Applicants submit that the specification that any GM-CSF having substantial identity would be expected to work in the methods of the invention. In view of the present disclosure and the references incorporated therein, one of skill in the art would appreciate that Applicants were in possession of methods for neovascularization by administering GM-CSF. In addition, based on Applicants' disclosure and what formed part of the skilled person's common general knowledge at the time the application was filed, one skilled in the art would be able to make and use the invention across the entire scope of the claims without undue burden or experimentation. Accordingly, the written description rejection of claims 50, 53, 55-63, 65-68, 70, 72-78 and 84 should be withdrawn.

Rejection under 35 U.S.C. §103

Claims 50, 52, 55-63, 65-68, 70, 72-73, 75, and 84 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,332,671 ("Ferrara") in view of Bussolino et al. (Path. Res. Pract., 190:834-839) ("Bussolino") and Orazi et al., (Blood, 79(10):2610-2619). Claims 50, 52, 55-63, 65-68, 70, and 84 are directed to methods for inducing formation of new blood vessels in a mammal having chronic or acute ischemia by administering an effective amount of a vascular endothelial growth factor (VEGF), or an effective fragment thereof, and a granulocyte-macrophage colony stimulating factor (GM-CSF). Claims 72-78 are directed to methods of reducing or preventing the severity of blood vessel damage in a mammal having chronic or acute ischemia an effective amount of a vascular endothelial growth factor (VEGF), or an effective fragment thereof, and a granulocyte-macrophage colony stimulating factor (GM-CSF). Applicants respectfully disagree and traverse the rejection.

To properly determine a prima facie case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is

important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." Id. Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007).

Ferrara

Ferrara describes the *in vitro* expression of VEGF in cultured cells, and an assay for VEGF activity in chicken eggs (column 27, lines 22-43). Specifically, Ferrara describes the application of VEGF to the chorioallantoic membrane of a fertilized chicken egg (column 27, lines 22-43). Based on the growth of blood vessels within the egg, Ferrara suggests that VEGF may be used to treat vascular trauma. Ferrara fails to teach or suggest the use of VEGF in treating chronic or acute ischemia. In fact, Ferrara fails to describe the use of VEGF to **induce blood vessel growth** in any mammalian system.

Ferrara merely teaches that "VEGF [was] efficacious in promoting the **proliferation of fetal and adult bovine ... endothelial cells**" in culture (Example 3, column 27, lines 12-20). Based on these results, Ferrara speculates that "VEGF **may potentially** play a role as a soluble mediator of endothelial cell growth and angiogenesis." [emphasis added; column 30, lines 25-27). The *in vitro* effects on endothelial cell proliferation observed by Ferrara would not motivate one of skill in the art to administer VEGF for the treatment of any mammalian condition, much less for the inducement of new blood vessel growth for the treatment of chronic or acute ischemia or for reducing or preventing the severity of blood vessel damage related to chronic or acute ischemia. To remedy the deficiencies of Ferrara, the Office cites Bussolino and Orazi.

Bussolino

Bussolino provides a review of the role of hematopoietic cytokines on stromal cells and endothelial cells. Bussolino fails to remedy the deficiencies of Ferrara because Bussolino fails to describe methods for inducing new blood vessel growth or reducing or preventing the severity of blood vessel damage using VEGF and GM-CSF. As noted on pages 9 and 10 of the Office Action, Bussolino states that "The primary effect of GM-CSF and G-CSF on vasculature *in vivo*

is the stimulation of the angiogenesis process." (page 836, column 2, first full paragraph, first sentence) Like Ferrara, Bussolino fails to teach or suggest that VEGF or GM-CSF should be administered to induce new blood vessel growth for the treatment of ischemia or to treat or prevent blood vessel damage related to ischemia. Moreover, Bussolino fails to teach or suggest that VEGF and GM-CSF should be administered in combination. Therefore, Bussolino fails entirely to remedy the deficiencies of Ferrara.

Orazi

Orazi describes the effect of GM-CSF on bone marrow following chemotherapy. Orazi observed that "After cytokine treatment, the BM [bone marrow] vascular network was much increased and showed branching, tortuosity, and dilation" (page 2615, column 2, last paragraph, second sentence). Like Ferrara and Bussolino, Orazi fails to teach or suggest that VEGF or GM-CSF should be combined, or that either VEGF or GM-CSF should be administered to induce new blood vessel growth to treat acute or chronic ischemia or to prevent ischemia related blood vessel damage. Thus, Orazi fails to remedy the deficiencies of Ferrara and Bussolino.

In sum, the combination of references cited by the Office fail to teach or suggest each element of Applicants' claims, and cannot be used to support a *prima facie* showing of obviousness. Importantly, none of the references, alone or in any combination, teaches or suggests that VEGF and GM-CSF should be administered in combination to induce new blood vessel growth to treat acute or chronic ischemia or to prevent ischemia related blood vessel damage. Accordingly, the obviousness rejection should be withdrawn.

Double Patenting Rejections

Claims 50, 55-63, 65-67 and 84 are provisionally rejected under the judicially created doctrine of double patenting over claims 3-4 and 11 of U.S. Patent No. 5,980,887. Claims 50, 52, 55-63, 65-68, 70, 72-78 and 84 are rejected on the grounds of nonstatutory obviousness-type double patenting as unpatentable over claims 1-11 of U.S. Patent No. 5,980,887 in view of Bussolino and Asahara. Claims 50, 55-63, 65-67 and 84 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 49-52, 54-59, 62-65, and 68-69 of co-pending U.S. Patent Application No. 10/696,391. Claims 50, 55-63, 65-67 and 84 are provisionally rejected under the judicially created doctrine of obviousness-type

double patenting over claims 49, 58-60, and 68-70 of co-pending U.S. Patent Application No. 10/714,574.

Applicants respectfully traverse the rejections. Applicants will address the double patenting rejections of the claims upon a finding that the claims (that will be pending upon entry of the amendments presented herein) are in condition for allowance, but for the instant double patenting rejection. As the Office has not yet indicated any allowed claims, Applicants have not addressed the obviousness-type double patenting rejections.

CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the application with claims 50, 52, 55-63, 65-68, 70, 72-78, and 84 presented herein. In advance of the issuance of a final Office Action, Applicants invite the Examiner to call the undersigned at the telephone number indicated below to schedule an interview.

Applicants submit this paper in response to the Office Action dated February 26, 2009, in the above-referenced patent application with a Petition for a One-month Extension of Time and the requisite fees based on large entity status. Applicants believe that no other fees are due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **04-1105**, under Order No. 47624DIV (71417).

Dated: June 26, 2009

Respectfully submitted,

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